

Application No. 10/578,171  
Amendment dated September 21, 2011  
Reply to Office Action of March 21, 2011

**Remarks/Arguments**

Reconsideration and allowance of the above-referenced application are respectfully requested.

**Statement of Substance of Interview**

The applicants acknowledge with appreciation the courtesy of the Examiner in holding a telephone conference with the applicants and their counsel on July 20, 2011. The claim amendments and Remarks/Arguments address the new matter and prior art concerns raised by the Examiner in the Office Action. The Interview Summary issued on July 28, 2011 accurately describes the substance of the telephone interview.

**Status of the Claims**

Claims 1, 2, 9, 14-16, 19, 25, 28, 37, 39, 51-52, 59, 66 and 68-90 are pending. Claims 1, 9, 16, 19, 28, 37, 39, 59, 66, 68, 70-71, 75-78 and 83 are amended and new claims 87-90 are added. Basis for the amendments and new claims can be found in various parts of the specification, including but not limited to the portions set forth on Table 1 below:

Table 1

Indep. Claim 1	Paras. 145, 155 (sensor implanted in biological tissue), 7 (analyte permeable coatings), 146-147 (analyte permeable coatings (e.g. Nafion) do not prevent sensing (and therefore must allow analytes through)); 146, 148 (biological matrix is exterior to sensor having analyte permeable coating (e.g. Nafion) on outer surface); 145, 148, 171 (increased sensor functionality (period of sensitivity); inhibit inflammation and promote neovascularization) 141, 144, 145, Fig. 20, 21, 24 (extend sensor lifespan by
----------------	---

Application No. 10/578,171  
Amendment dated September 21, 2011  
Reply to Office Action of March 21, 2011

	at least one day)
Indep. Claim 28	Paras. 145, 155 (sensor implantable in biological tissue), 7 (analyte permeable coatings), 146-147 (analyte permeable coatings (Nafion) do not prevent sensing (and therefore must allow analytes through)); 146, 148 (biological matrix is exterior to sensor having analyte permeable coating (Nafion) on outer surface); 145, 148, 171 (increased sensor functionality (period of sensitivity); promote neovascularization) 141, 144, 145, Fig. 20, 21, 24 (extend sensor lifespan by at least one day)
Indep. Claim 37	Paras. 145, 155 (sensor implanted in biological tissue); 7 (analyte permeable coatings), 146-147 (analyte permeable coatings (Nafion) do not prevent sensing (and therefore must allow analytes through)); 146, 148 (biological matrix exterior to sensor having analyte permeable coating (Nafion) on outer surface); 167-previously amended (biological matrix increasing sensor sensitivity, thereby increasing sensor functionality) 145, 148, 171 (cells supported by matrix increasing lifespan of sensor) 141, 144, 145, 167, Fig. 20, 21, 24, Fig. 38 (extend sensor lifespan by at least one day)

Application No. 10/578,171  
Amendment dated September 21, 2011  
Reply to Office Action of March 21, 2011

Indep. Claim 78	Paras. 7 (analyte permeable coatings), 146-147 (Nafion coatings allow analytes through); 135, 149, 166 (biological tissue, ex ova CAM model, mouse tissue); 148-149 (matrix exterior to Nafion coated sensor); 167-previously amended and Fig. 38 (increased sensor functionality) 167, Fig. 38 (extend sensor functionality by at least one day)
Dep. Claims 9 and 39	Para. 171
Dep. Claim 70, 71, 86	Para. 171 etc. ( <u>neovascularization</u> – new (biological) tissue)
Dep. Claims 16, 19, 59, 66 68, 75-77 and 83	Amended to be consistent with an independent claim
Dep. Claims 87-90 (New)	Para. 171 (cells that limit inflammation); 77-78 (cells that control fibrosis) Figs. 20-21, 24 and 38, and paras. 141, 144, 145 and 167 (extend sensor functionality (period of sensitivity) by at least three days)

### **Claim Rejections – 35 U.S.C. § 112**

Claim 86 is rejected under 35 U.S.C. § 112 as lacking antecedent basis. More particularly, the Office Action contends that the term “the biological tissue” in claim 86 (which depends from claim 70) lacks antecedent basis. Claims 70 and 86 are amended to use the term “new tissue” in order to be distinguished from the amended versions of the independent claims that refer to “biological tissue.” Reconsideration is requested.

Application No. 10/578,171  
Amendment dated September 21, 2011  
Reply to Office Action of March 21, 2011

Claims 1, 2, 9, 14-16, 19, 25, 28, 37-39, 51, 59, 66 and 68-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Reconsideration is requested.

The Office Action requests that the applicant point to the portions of the specification that support contact between the matrix and both the outer surface of the implantable device and the biological system. Independent claims 1, 28, 37 and 78 are amended to clarify the relationship of the recited components in order to overcome this rejection. The independent claims now provide that the outer surface of the sensor includes an analyte permeable coating (such as (but not limited to) the Nafion coating used in some of the Examples) in contact with the matrix. The analyte permeable coating is recited as a part of the sensor itself, and the biological matrix is exterior to the sensor. The independent claims as amended also provide that biological tissue is in contact with the matrix. This configuration is supported by Fig. 1 (showing the sensor 10 within the matrix material 22) and paragraphs 164, 166 and 167 which describe implanting sensors having an outer surface of an analyte permeable coating (Nafion) in biological tissue without a biological matrix (the “control mice”) and with a biological matrix (Matrigel treated mice). Furthermore, paragraph 144 describes sensors implanted on CAMs. Sensor preparation is described in paragraph 142, which indicates that the sensors are coated with an analyte permeable coating (Nafion) before being placed in a biological matrix, as described in paragraph 144. Thus, the applicants submit that the section 112 rejection is overcome. Reconsideration is requested.

#### **Claim Rejections – 35 U.S.C. § 102**

Claims 1, 2, 9, 14-16, 19, 25, 28, 37, 39, 51, 66, 68-70, 72, 73, 75-82 and 84 are rejected under 35 U.S.C. 102(e) as being anticipated by Sayler et al. (U.S. Patent No.: 6,673,596; filed Dec. 2, 1999. Reconsideration is requested.

The March 21, 2011 Office Action (page 7) states that “there is no requirement in the claims that the biological matrix is in contact with both an outer surface [of the sensor] and body tissue. Instead, the claims merely recite that the biological matrix

must be in contact with the outer surface of the device and a “biological system.” In response to this contention, the applicant has amended independent claims 1, 28, 37 and 78 such that the biological matrix is “exterior to the sensor.” Furthermore, the amended independent claims provide that the biological matrix is in contact with both biological tissue (e.g., a chick embryo culture system or mouse tissue in the examples) and the analyte permeable coating on the outer surface of the sensor. In contrast, the “cells” of Sayler are inside the sensor (required because they are bioreporter cells).

Page 7 of the Office Action states that in the prior version of the claims, “what exactly constitutes the ‘outer surface of the implantable device’ may be very broad.” In response, the applicant has amended the independent claims to recite the outer surface of the sensor, rather than the outer surface of the implantable device. As indicated above, the independent claims are amended to provide that the biological matrix is exterior to the sensor. The Saylor reference does not have Matrigel exterior to the sensor, but instead has Matrigel inside the sensor.

The Office Action contends (on page 8) that the blood plasma in contact with Saylor’s sensor constitutes a “biological system.” In order to even further distinguish the claims of the present application, the applicant has amended independent claims 1, 37 and 78 to provide that the sensor is implanted in biological tissue and that the matrix is in contact with the biological tissue (i.e. the tissue in which the sensor is implanted). Claim 28 as amended provides that the sensor and the matrix (which is exterior to the sensor) are implantable in biological tissue. According to col. 23 of Saylor, the bioengineered cells of Saylor are inside the sensor and therefore are inside the semi-permeable membrane. In contrast, in the independent claims of the present application, the cells are exterior to the sensor. Claims 28 and 37 also provides that the cells promote neovascularization of the biological tissue. There is no disclosure or suggestion in Saylor of a cell-containing matrix exterior to the sensor (independent claims 1, 28 and 37), or of an exterior matrix containing cells that promote neovascularization (independent claim 28).

Col. 17 of Sayler indicates that the BBIC is enclosed in a biocompatible housing with a semi-permeable membrane covering the bioreporter region. There is no disclosure or suggestion that the Sayler membrane contains cells of the type recited in independent claims 1, 28 and 37 of the present application exterior to the semi-permeable membrane. The applicants respectfully submit that the coating described in Sayler compares to the Nafion coating used in the Examples of the present application, and is used to form the outer surface of the Sayler sensor. Col. 17, lines 57-67 discuss applying coatings that promote biocompatibility. There is no disclosure of such coatings containing the cell-matrix structure (independent claims 1, 28 and 37). Furthermore, there is no disclosure of such coverings containing a matrix containing cells that promote neovascularization (claim 28). With respect to claim 78 of the present application, there is no disclosure or suggestion in Sayler of a matrix exterior to the sensor that comprises a cell culture derived basement membrane.

Col. 25, lines 14-37 of Sayler provide that "host-rejection effects can be minimized by immunoisolation techniques." Synthetic hydrogels such as polyvinyl alcohol hydrogel bags are described that will keep the cells inside the sensor. In contrast, the cells recited in independent claims 1, 28 and 37 of the present application are exterior to the sensor.

Page 9 of the Office Action contends that the limitation of "extending the functional lifespan of the sensor" would be met by a lifespan extension of a few minutes. In order to overcome this rejection, the independent claims are amended to provide that sensor functionality is extended by at least one day. Dependent claims 89-90 recite that sensor functionality is increased by at least three days. In Sayler, "cells derived from the patient" that are referred to at the bottom of page 9 of the Office Action are located inside the sensor.

Thus, independent claims 1, 28, 37 and 78 are patentable over Sayler. Claims 2, 9, 14-16, 19, 25, 39, 51, 66, 68-70, 72, 73, 75-77, 79-82 and 84 depend directly or indirectly upon one of the independent claims and are patentable over Sayler for the same reasons. Reconsideration is requested.

**Claim Rejections – 35 U.S.C. § 103**

Claims 1, 2, 9, 14-16, 19, 25, 28, 37-39, 51, 59, 66, and 68-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sayler et al. (U.S. Patent No.: 6,673,596; filed Dec. 2, 1999), in view of Soykan et al. (U.S. Patent Application Publication No. 2001/0000802). Reconsideration is requested.

Independent claims 1, 28, 37 and 78 as amended are distinguished from Sayler for the reasons discussed above in connection with the 102 rejection. Sayler does not disclose a structure with a biological matrix exterior to the sensor and in contact with both the outer surface of the sensor and biological tissue (the matrix being described as cell culture derived basement membrane in claim 78). Furthermore, Sayler does not disclose cells in the biological matrix exterior to the sensor (claims 1, 28, and 37). Soykan does not make up for these deficiencies. According to pages 13-14 of the Office Action, Soykan is cited as showing the use of “endothelial cells transformed with a VEGF gene in the implant of Sayler et al.” However, there is no teaching or suggestion in either reference of the desirability of combining the references in the manner suggested in the Office Action. Furthermore, if the two references were combined, the combination would not result in the system claimed in the present application.

More particularly, page 11 of the Office Action states that “[w]hile Sayler et al. do not specifically describe the cells as inducing cellular growth and neovascularization . . . such was known in the prior art.” The Office Action further contends that it would have been obvious to one having ordinary skill in the art, based upon a combination of Sayler and Soykan, to genetically alter the cells (which are inside the Sayler sensor) “to induce cellular growth and neovascularization.” The applicants point out that there is no mention of neovascularization in Sayler. Furthermore, there is no indication in Sayler that out of all the possible tissue responses that someone with ordinary skill in the art would consider, they would decide to induce blood vessel formation. The applicant respectfully submits that one would not want to induce neovascularization inside a sensor, as this would result in painful removal of the sensor and would likely destroy

Application No. 10/578,171  
Amendment dated September 21, 2011  
Reply to Office Action of March 21, 2011

sensor function. Finally, if the teaching of the two cited references were combined, the cells would still be on the inside, rather than the outside of the sensor. Thus, the combination of Sayler and Soykan teaches away from inducing neovascularization due to inserted cells.

The Office Action contends that the Declaration filed on March 15, 2010 does not provide any evidence that if persons skilled in the art who were presumably working on the problem of sensor lifespan knew of the teachings of the above cited references, they would still be unable to solve the problem. In response, the applicants respectfully submit that for the reasons discussed above, even if one having ordinary skill in the art in November of 2003 had read the Sayler and Soykan references, these references could not be combined in a manner that renders obvious the claims of the present application, as the cells of Sayler are inside the sensor. Furthermore, while the March 2010 Declaration does indicate that transdermal glucosensors are now on the market that are approved for up to 7 days, this was not the case when the present application was filed in 2003. As indicated in the attached pages printed from an FDA internet site, to the best of the applicant's knowledge, the first FDA approval for continuous glucose monitoring systems was March 24, 2006, which is well after both the filing date and the publication date of the present application. Furthermore, the 2006 system was approved for use for up to 72 hours (three days). The reference in the 2010 Declaration to 7 day systems was a reference to a system that was approved on May 31, 2007, which is more than three years after the filing date of the present application. The Examiner has not pointed to any art dated before the applicant's 2003 filing date that would lead one to think that the applicant's work represents an improvement on the results produced by others, as opposed to the work of others being inspired by the work of the applicants that is disclosed in this 2003 application.

Thus, the applicants submit that independent claims 1, 28, 37 and 78 are patentable over the cited references. Furthermore, dependent claims 2, 9, 14-16, 19, 25, 38-39, 51, 59, 66, 68—77 and 79-86 are non-obvious over the combination of

Application No. 10/578,171  
Amendment dated September 21, 2011  
Reply to Office Action of March 21, 2011

Sayler and Soykan for the same reasons as are applied to the independent claims. Reconsideration is requested.

The applicants contend that the claims in their amended form are patentable over the references. However, if the Examiner believes that additional amendments of a minor nature are need in order to place the claims in allowable form, he is asked to telephone the undersigned at the number provided below.

In view of the above, the applicants believe that this application is in condition for allowance and such a Notice is respectfully solicited.

Respectfully submitted,

Ulrike W. Klueh et al.

By: Diane F. Covello

Diane F. Covello  
Registration No. 34,164  
Alix, Yale & Ristas, LLP  
Attorney for Applicant

Date: September 21, 2011  
750 Main Street, Suite 1400  
Hartford, CT 06103-2721  
Telephone: 860-527-9211  
Our Ref: MTT/101/PC/US  
DFC/eg

Encl. Overviews of March 24, 2006 and May 31, 2007 Continuous Glucose Monitoring System Approvals